Ptch2 mediates the Shh response in Ptch1-/- cells.

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Public Summary:
This article investigates the molecular mechanism of the Hedgehog signaling cascade, one of the most fundamental signaling processes in embryogenesis. The Hedgehog (Hh) signaling response is regulated by the interaction of three key components that include the sonic hedgehog (Shh) ligand, its receptor patched 1 (Ptch1) and the pathway activator smoothened (Smo). Using in vitro and chick embryo models in which key regulatory components of the Hedgehog pathway, the sonic hedgehog Shh ligand and its receptors patched 1 (Ptch1) and patched 2 (Ptch2) were inactivated, we found that Ptch1(-/-) cells remain sensitive to Shh and show a strong Shh ligand dependent upregulation of the Hh signaling response. We show that at early developmental stages, Ptch2 functions to suppress Shh signaling. Cells in which both Ptch1(-/-) and Ptch2(-/-) are inactivated cannot further activate the Shh response, demonstrating that Ptch2 mediates the response to Shh in the absence of Ptch1.

Scientific Abstract:
The Hedgehog (Hh) signaling response is regulated by the interaction of three key components that include the sonic hedgehog (Shh) ligand, its receptor patched 1 (Ptch1) and the pathway activator smoothened (Smo). Under the prevailing model of Shh pathway activation, the binding of Shh to Ptch1 (the key Shh receptor) results in the release of Ptch1-mediated inhibition of Smo, leading to Smo activation and subsequent cell-autonomous activation of the Shh response. Consistent with this model, Ptch1(-/-) cells show a strong upregulation of the Shh response. Our finding that this response can be inhibited by the Shh-blocking antibody 5E1 indicates that the Shh response in Ptch1(-/-) cells remains ligand dependent. Furthermore, we find that Shh induces a strong response in Ptch1(-/-);Shh(-/-) cells, and that Ptch1(-/-) fibroblasts retain their ability to migrate towards Shh, demonstrating that Ptch1(-/-) cells remain sensitive to Shh. Expression of a dominant-negative Ptch1 mutant in the developing chick neural tube had no effect on Shh-mediated patterning, but expression of a dominant-negative form of patched 2 (Ptch2) caused an activation of the Shh response. This indicates that, at early developmental stages, Ptch2 functions to suppress Shh signaling. We found that Ptch1(-/-);Ptch2(-/-) cells cannot further activate the Shh response, demonstrating that Ptch2 mediates the response to Shh in the absence of Ptch1.